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Application No.	:	**2,501,295**
Owner	:	REGENTS OF THE UNIVERSITY OF CALIFORNIA; CATALYST BIOSCIENCES, INC.
Title	:	**METHODS OF GENERATING AND SCREENING FOR PROTEASES WITH ALTERED SPECIFICITY**
Classification	:	A61K 38/48 (2006.01)
Your File No.	:	**51205-75 EAH:pw**
Examiner	:	**André Pilon**

YOU ARE HEREBY NOTIFIED OF A REQUISITION BY THE EXAMINER IN ACCORDANCE WITH SUBSECTION 30(2) OF THE *PATENT RULES*. IN ORDER TO AVOID ABANDONMENT UNDER PARAGRAPH 73(1)(*a*) OF THE *PATENT ACT*, A WRITTEN REPLY MUST BE RECEIVED WITHIN 6 MONTHS AFTER THE ABOVE DATE.

This application has been examined taking into account the:

Description,	pages 1-3 and 5-54, as originally filed; the sequence listing (pages 1-2), as received with the letter of September 18, 2006 during the international phase; pages 4, 4a-4f, as received with the letter of August 21, 2009 during the national phase;
Claims,	1-75, as received with the letter of August 21, 2009 during the national phase; and
Drawings,	pages 1-7, as originally filed.

This application has been examined taking into account applicant's correspondence on prior art received in this office on August 10, 2008 and August 21, 2009.

The number of claims in this application is 75.

The examiner has identified the following subject-matter:

Group A - Claims 1-55, 71 (partly) and 73-75, are directed to a modified protease comprising mutations in the wildtype protease scaffold that alter the cleavage activity and/or specificity of the protease for a target protein that is involved in a disease or pathology, a method of obtaining such protease and their use;

The proteases are divided into six groups: the serine proteases, threonine proteases, cysteine proteases, aspartate proteases, metalloproteases and the glutamic acid proteases that do not share a common "protease scaffold". Thus, within **Group A**, the application contains claims that are directed to more than one group that are not so linked as to form a single inventive concept. 2

Group B - Claims 56-70, 71 (partly) and 72 are directed to a method of producing candidate <u>therapeutics</u> that inactivate or modulate the activity of a target protein, or that cleave a target protein, that is associated or that causes a disease or pathology. 3

As the application is apparently directed to a plurality of inventions, the examiner has proceeded on the presumption that the applicant will elect the claims of **Group A**, a modified protease comprising mutations in a wildtype **serine** protease scaffold that alter the cleavage activity and/or specificity of the modified protease for a target protein that is involved in a disease or a pathology. This presumption does not affect the applicant's right to elect, one time, a different invention for prosecution. The scope of the search and examination of the claims was therefore restricted to the subject-matter of the claims of **Group A** as they relate to serine proteases (claims 1-55, 71 (partly) and 73-75). 4

The search of the prior art has revealed the following:

<u>References Applied:</u>

<u>Publications</u>

A Harris, J.L. et al. Journal of Biological Chemistry ¤ (1998)Vol. 273, No. 42, pp. 27364-27373

B Bornscheuer, U.T. and Pohl, M. Current Opinion in Chemical Biology ¤ (2001)Vol. 5 No. 2, pp. 137-143

C Olsen, M. et al., Current Opinion in Biotechnology ¤ (2000)Vol. 11, pp. 331-337

<u>United States Patent</u>

D US 5486602 ¤ (1996) Sambrook, J.F. et al.

¤ citation stemming from a foreign search report

Harris, J.L. et al., disclose the definition and identification of granzyme B substrate specificity. Granzyme B is a protease involved in the induction of rapid target cell death by cytotoxic lymphocytes. By using the combinatorial methods of synthetic substrate libraries and substrate-phage display, an optimal substrate for granzyme B that spans over six subsites was determined. 5

Bornscheuer, U.T. and Pohl, M., disclose that the efficient application of biocatalysts requires the availability of suitable enzymes with high activity and stability under process conditions, desired substrate selectivity and high enantioselectivity. However, wild-type enzymes often 6

need to be optimized to fulfill these requirements. Two rather contradictory tools can be used on a molecular level to create tailor-made biocatalysts: directed evolution and rational protein design.

Olsen, M. et al., review methods of high-throughput screening of enzyme library where libraries of mutant genes can be generated by a variety of methods such as the use of degenerate oligonucleotides and chemical mutagenesis. These mutant libraries can then be interrogated for catalytic activity. 7

Sambrook, J.F. et al., disclose serine protease mutants of the chymotrypsin superfamily that are resistant to inhibition by their cognate inhibitors, and genes that encode the same. The invention also relates to serine protease inhibitor mutants that inhibit the serine protease mutants of the invention, and genes that encode the same. The serine protease mutants and serine protease inhibitor mutants are useful as, e.g., pharmacological agents. 8

The examiner has identified the following defects in the application:

Claims 1-55, 71 (partly) and 73-75 do not comply with section 28.3 of the *Patent Act*. The subject matter of these claims would have been obvious on the claim date to a person skilled in the art or science to which they pertain having regard to Bornscheuer, U.T. and Pohl, M., or Sambrook, J.F. et al., or Olsen, M. et al., in view of Harris, J.L. et al. 9

Bornscheuer, U.T. and Pohl, M., disclose that the efficient application of biocatalysts requires the availability of suitable enzymes with high activity and stability under process conditions, desired substrate selectivity and high enantioselectivity. However, wild-type enzymes often need to be optimized to fulfill these requirements. Two rather contradictory tools can be used on a molecular level to create tailor-made biocatalysts: directed evolution and rational protein design. Sambrook, J.F. et al., disclose serine protease mutants of the chymotrypsin superfamily that are resistant to inhibition by their cognate inhibitors, and genes that encode the same. The present invention also relates to serine protease inhibitor mutants that inhibit the serine protease mutants of the present invention, and genes that encode the same. The serine protease mutants and serine protease inhibitor mutants are useful as, e.g., pharmacological agents. Olsen, M. et al., review methods of high-throughput screening of enzyme library where libraries of mutant genes can be generated by a variety of methods such as the use of degenerate oligonucleotides and chemical mutagenesis. These mutant libraries can then be tested for catalytic activity. 10

Harris, J.L. et al., disclose the definition and identification of granzyme B substrate specificity. Granzyme B is a protease involved in the induction of rapid target cell death by cytotoxic lymphocytes. 11

Thus, it is clear the prior art is replete with examples of methods of providing mutant enzymes with improved activity and/or specificity. The Olsen, M. et al., and the Bornscheuer, U.T. and Pohl, M., reviews outlines a number of methods for producing improved biocatalysts. In addition, Harris, J.L. et al., disclose that Granzyme B is a protease involved in the induction of rapid target cell death by cytotoxic lymphocytes and that the granzyme B enzyme belongs to a 12

subclass of serine proteases displaying the chymotrypsin fold. It would thus have been obvious to one skilled in the art to use the enzyme screening methods of Bornscheuer, U.T. and Pohl, M., or Sambrook, J.F. et al., or Olsen, M. et al., to provide protease of increased activity and/or specificity against targets such as granzyme B, a key mediator of cell death, and other members of that protease family.

The application does not comply with subsection 36(1) of the *Patent Act*. The claims are directed to a plurality of alleged inventions as indicated above. According to subsection 36(2) of the *Patent Act*, after limiting the claims of the present application to one invention only, the applicant may make any other invention disclosed the subject of a divisional application. The applicant is advised that once an election has been made, further prosecution of the present application will be limited to the invention so elected. 13

The applicant is reminded that the requirement for unity of invention shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features. The expression "special technical features" shall mean those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art. The presently claimed subject matter does not fulfil the above requirements on unity of invention. In view of the disclosure of the present application, the technical problem to be solved is to provide proteases with altered specificity and their use for treating diseases. The available prior art discloses at least one solution to said technical problem as presented in Harris, J.L. et al. Therefore, the solution to the problem is not novel. It follows that there is no common special technical feature that would define an appreciable contribution over the prior art. 14

Claims 1-28, 73-75 do not comply with section 84 of the *Patent Rules*. The claimed modified protease is a hypothetical compound for which applicant has no support, and thus applicant cannot define said modified protease beyond an insufficient statement of the desired result. Applicant has not invented the hypothetical modified protease and is requested to omit claims directed to said modified protease. 15

In view of this, it follows that this application does not comply with subsection 27(3) of the *Patent Act*. The specification does not correctly and fully describe the claimed modified protease. 16

Claims 1 and 17 are indefinite and do not comply with subsection 27(4) of the *Patent Act*. It is not clear what the applicant means by "comprising mutations in a wildtype protease scaffold that alter the cleavage activity and/or specificity..." as the word "alter" does not serve to clearly and explicitly define the changes to the activity and/or specificity of the mutant protease. In addition, the modified protease of claims 1 and 17 are defined by the process by which they are made. However, that process is vague, incomplete and inaccurate as the wildtype protease is not defined. A protease is any enzyme that conducts proteolysis , that is, begins protein catabolism by hydrolysis of the peptide bonds that link amino acids together in a polypeptide chain, which form a molecule of protein. The proteases are divided into six groups: the serine proteases, threonine proteases, cysteine proteases, aspartate proteases, metalloproteases and the glutamic acid proteases. Thus, it is not clear which protease can be used in the method. 17

Further, the statement that "the target protein is involved in a disease or pathology" is not sufficient to clearly and specifically define the target protein. Finally, the "activity" of the target protein is not defined.

Claims 1-6, 8, 16-19, 21-43, 45-55 and 75 do not comply with section 84 of the *Patent Rules*. The applicant has no support for **modified aspartic proteases, cysteine proteases** or **metalloproteases** or use of said proteases. The applicant has no support for the use of a protease as a scaffold for preparing a therapeutic that cleaves a target involved in a disease or pathology other than granzyme B. The applicant provides a laundry list disclosure of every possible protease and hypothesizes that they could be used as therapeutics. However, a laundry list does not constitute a proper disclosure in that some exemplary support is needed. As stated above, proteases are a family of enzymes made up of 6 distinct sub-families with different properties. In addition, the applicant has no support for a modified protease that alter the cleavage activity and/or specificity to a **target** protein, listed in claims 24, 32, 43 and 75, other than a substrate for granzyme B, TNF, the TNF receptor and caspase 3 as target. It follows that one skilled in the art could not produce the modified proteases having altered activity or specificity against a multitude of different targets without undue experimentation. 18

In view of this, it follows that this specification does not comply with subsection 27(3) of the *Patent Act*. The specification does not correctly and fully describe the invention and its operation or use, so as to enable any person skilled in the art to practice the invention. 19

Claims 4, 6-10, 13-17, 20, 21, 26, 27 are indefinite and do not comply with subsection 27(4) of the *Patent Act*. The expression "protein scaffold" has no antecedent. In addition, it is not clear if the applicant is referring to the "wildtype protein scaffold" of claim 1 or to another "protein scaffold". 20

Claims 22, 31, 41 and 74 do not comply with section 84 of the *Patent Rules*. The applicant has no support for a modified protease wherein the modified protease is a therapeutic for a pathology selected from the group of pathologies listed in claims 22, 31, 41 and 74. 21

In view of this, it follows that this specification does not comply with subsection 27(3) of the *Patent Act*. The specification does not correctly and fully describe the invention and its operation or use, so as to enable any person skilled in the art to practice the invention. 22

Claim 28 is indefinite and does not comply with subsection 27(4) of the *Patent Act*. The expression "scaffold protease" has no antecedent. 23

Claims 37-39 are indefinite and do not comply with subsection 27(4) of the *Patent Act*. It is not clear if the "scaffold protease" of claims 38 and 39 is the same as the "wildtype scaffold protease" of claim 33. Clarification is needed. 24

Claims 39 and 44 are indefinite and do not comply with subsection 27(4) of the *Patent Act*. The expression "scaffold protease" has no antecedent in claim 33. 25

In view of the foregoing defects, the applicant is requisitioned, under subsection 30(2) of the *Patent Rules*, to amend the application in order to comply with the *Patent Act* and the *Patent Rules* or to provide arguments as to why the application does comply.

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